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| APPLICATION NO.  | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 09/255,963   | 02/23/1999  | PETER X. MA          | UMJ-101-A           | 9213             |
| 29296  | 7590        | 10/24/2003           | EXAMINER            |                  |
| JULIA CHURCH DIERKER<br>DIERKER & GLASSMEYER, P.C.<br>3331 W. BIG BEAVER RD., SUITE 109<br>TROY, MI 48084-2813 |             |                      | KAUSHAL, SUMESH     |                  |
|  |             |                      | ART UNIT            | PAPER NUMBER     |
|  |             |                      | 1636                |                  |

DATE MAILED: 10/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Advisory Action**

Applicati n No.

09/255,963

Applicant(s)

MA, PETER X.

Examiner

Sumesh Kaushal Ph.D.

Art Unit

1636

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08/28/03 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.  
2. ☐ The proposed amendment(s) will not be entered because:  
(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ they raise the issue of new matter (see Note below);  
(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_.

3. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.  
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.  
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.  
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_.

Claim(s) objected to: \_\_\_\_\_.

Claim(s) rejected: 1-20,22,23,25-38 and 40-55.

Claim(s) withdrawn from consideration: \_\_\_\_\_.

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.  
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.  
10. ☐ Other: \_\_\_\_\_

  
JEFFREY FREDMAN  
PRIMARY EXAMINER

Continuation of 3. Applicant's reply has overcome the following rejection(s): Claims 1-20, 22-23, 25-30, 32-38, 40-55 under 35 U.S.C. 112, second paragraph issues.

Continuation of 5. does NOT place the application in condition for allowance because: Claims 1-20, 22-23, 25-38 and 40-55 are rejected under 35 U.S.C. 103(a) regarding prior art issues for the same reasons of record as set forth in the office action mailed on 05/28/03.

Response to arguments :

Applicant argues that none of the cited references teach or suggest selective size control of a three-dimensional hydrogel system by varying cation concentration of a separate medium into which it is introduced. The applicant argues that Draget is silent as to transferring a hydrogel into a medium. Applicant argues that the '343 patent controls the hydrogel system by a mechanical means. Applicant further argues that Martinsen is not describing selective control of the size of a hydrogel. The applicant argues that Martinsen was published in 1959 and researchers in tissue engineering have been searching for means of controlling the size of a formed hydrogel however, prior to applicant's invention, these efforts had been unsuccessful. The applicant argues that the office was using hindsight to assume that Martinsen was teaching volume control of a non-bead uniformly cross-linked hydrogel. The applicant concluded that the chemistry of controlling hydrogel size is unpredictable.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In instant case Draget clearly teaches that variation in calcium ion concentration results in the formation of hydrogels with distinct characteristics. Martisen teaches that evaluation of stability of Ca-alginate gel beads towards Na<sup>+</sup> ions by transferring gels beads to solutions containing different concentrations of CaCl<sub>2</sub> (0.001M-0.05M) and measuring the bead volume (shrinkage) every 24 hours for 3 days (page 81 col.1 para.1). The cited art teaches that gel strength and shrinkage is the function of CaCl<sub>2</sub> concentration and gelling time (page 84, col.1-2, fig-7 and 8). In addition the cited art teaches that high gel strength, low shrinkage, high stability towards Na<sup>+</sup> ions and high permeability are the most advantageous factors for the immobilization of living cells (page 89, col.2). Furthermore given the broadest reasonable interpretation the invention as claimed clearly reads upon a bead structure comprising a cross-linked hydrogel system.

Hauselmann also teaches that the molar ratio of calcium ions to carboxyl groups in the gel determines the amount of cross-linking of the gel, as well as the amount of swelling and thus size of the gel (e.g, col 7, lines 29-46, & Figure 6a,b). Furthermore, Cao teach the method of making and using biodegradable calcium alginate gels with osteoblasts in vitro for implantation in vivo to generate bone growth. (see abstract)

Thus it would have been obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Draget and Martisen by introducing cells (osteoblasts) as taught by Hauselmann and Cao to the Ca-alginate hydrogels composition. One would have been motivated to do this to utilize the gel as a scaffold for cell growth and differentiation for tissue engineering. It would have been further obvious in view of Martisen to control the hydrogel shrinkage or swelling by transferring the hydrogels into the solutions that contain different concentration of calcium ions. One would also have been motivated to alter the calcium ion concentration and the ratio of calcium ions to alginate carboxyl groups in order to controlling the amount of gel swelling and shrinkage. One would have been motivated to control hydrogel shrinkage and swelling because these characteristics are highly desirable in tissues engineering for different applications. The invention pertaining to specific ion concentrations and the molar ratios that results in hydrogel swelling and shrinking are the result of effective variables, which could have been readily determined by one of ordinary skill in the art especially in view of Draget and Martisen. Therefore control of gel shrinkage by optimizing Ca<sup>2+</sup> and Na<sup>+</sup> concentrations is not unpredictable but is well within the reach of one of ordinary skill in the art especially in view of combined teaching of prior art of record. Thus the invention as claimed is prima facie obvious in view of cited art of record. .